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(54) **PHARMACEUTICAL FORMULATION OF A DIDEMNIN COMPOUND**

EINE DIDEMNIN VERBINDUNG ENTHALTENDE PHARMAZEUTISCHE FORMULIERUNG

FORMULATION PHARMACEUTIQUE D'UN COMPOSE DE DIDEMNINE

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Description

[0001] The present invention relates to a pharmaceutical formulation, and more particularly a pharmaceutical formulation of a didemnin compound.

THE BACKGROUND

[0002] US Patent 5,294,603 to Rinehart claims a pharmaceutical composition comprising a didemnin, in combination with a pharmaceutically acceptable carrier, excipient or diluent. In that patent, extensive results are given for testing for biological activity, notably assay results for cytotoxicity and antiviral activity.

THE PROBLEM

[0003] In practice, there are some difficulties in preparing pharmaceutical compositions of didemnin compounds suited for administration to patients, and there is especially a need for a stable parental pharmaceutical dosage form. More specifically, didemnin compounds such as dehydrodidemnin B, also known as aplidine, require mixing with bulking agents, such as mannitol, for optimal, stable preparation of pharmaceutical dosage forms, in particular lyophilised preparations,

[0004] Certain bulking agents for this purpose, such as mannitol, require water for solubilisation, while drugs such as aplidine are poorly soluble in water. However, drug delivery to patients requires resuspending of the lyophilised materials before use.

THE INVENTION

[0005] The present invention solves the problem by providing a pharmaceutical composition of a didemnin compound, comprising firstly a lyophilised didemnin preparation including water-soluble materials and secondly a reconstitution solution of mixed solvents. The mixed solvents comprise an aqueous solvent, with the water serving to dissolve the water soluble material and the other solvent serving to dissolve the didemnin compound.

PREFERRED EMBODIMENTS

[0006] The pharmaceutical formulation of this invention is typically a stable parental pharmaceutical dosage form suited for reconstitution for administration to patients as an antitumor treatment. The invention solves the problem for drugs such as aplidine, which must be presented as lyophilised mixtures of two or more substances soluble in incompatible solvents. It preferably provides, separately bottled or otherwise contained, a premixed three component surfactant/alkanol/water mixture of solvents. In order to allow for proper resuspension of such pharmaceutical dosage forms, the separately packaged solvent mixture is provided to be added to the dry lyophilised preparations containing the drug and water soluble substances such as mannitol, before administration for treatment of disease.

[0007] Preferred didemnin compounds for the pharmaceutical compositions of this invention include didemnins and didemnin derivatives, such as dehydrodidemnins, nordidemnins, didemnin congeners and didemnin analogs. The present invention is particularly directed at didemnins with limited water solubility, including for example dehydrodidemnin B, also known as aplidine.

[0008] The antitumour agent aplidine (dehydrodidemnin B) is a natural occurring cyclic depsipeptide isolated from the Mediterranean runicate *Aplidium albicans*. Aplidine has been characterised by using several chromatographic and spectrometric techniques. Solubility testing showed that aplidine exhibits poor aqueous solubility. Moreover, the long-term stability of aplidine in solution is currently unknown.

[0009] The lyophilised didemnin preparation is preferably prepared by freeze drying a didemnin/alkanol/water mix, especially using t-butanol as the alkanol. The alkanol/water mix suitably contains 25 to 60% v/v alkanol. A bulking agent such as mannitol can also be included, though other conventional water-soluble additives may be included, known to be of utility in the preparation of such lyophilised dosage forms.

[0010] The reconstitution solution preferably comprises a surfactant/alkanol/water mix, especially using a nonionic surfactant and ethanol as the alkanol. The surfactant is suitably 10 to 25% v/v of the mix; the alkanol is suitably 10 to 25% v/v of the mix; and the water is suitably 50 to 80% v/v of the mix.

EXAMPLES

[0011] Freeze-drying was performed from a 1.0 mg/ml solution aplidine in 40% v/v t-butanol in water for injection ("WFI) containing 25 mg/ml mannitol as bulking agent. Differential scanning calorimetry studies were conducted to determine the freeze-drying cycle parameters. The prototype, containing 1.0 mg aplidine and 25 mg mannitol per vial was found to be the optimal formulation in terms of solubility, length of the freeze-during cycle and dosage requirements.

[0012] A solution composed of 15/15/70% (v/v/v) Cremophor EL/ethanol absolute/WFI was found to the optimal reconstitution solution, Cremophor EL being a glycerol-polyethylene glycol ricinoleate available from BASF in Germany.

[0013] Dilutions of reconstituted product with normal saline up to 1:200 showed it to be stable for at least 24 hours after preparation. Quality control of the freeze-dried formulation demonstrated that the manufacturing process does not change the integrity of aplidine. Shelf-life data, available thus far, show that the formulation is stable for at least 6 months when stored at +4°C in the dark.

[0014] Thus, the preferred aplidine product of this invention is a dual-package containing:

an injection vial containing aplidine 1 mg/vial lyophilized product, and an injection vial containing 2 ml of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstruction solution.

[0015] The use of 15/15/70% (v/v/v) Cremophor EL/ethanol/water as reconstitution solution for a lyophilized product is unprecedented. Thus far, the combination of Cremophor EL/ethanol in commercial available products has been used exclusively as solution vehicle (e.g., taxol or cyclosporine).

[0016] The development of the Cremophor EL/ethanol/water vehicle provides a potent co-solvent/surfactant system which can be applied as reconstitution solution in future drug formulations and allows the addition of a water soluble bulking agent such as mannitol. Furthermore, by decreasing the relative amount of Cremophor EL, a less toxic vehicle is created.

[0017] The manufacturing procedure of the lyophilized product has also a special feature. Normally, freeze-drying of a drug is performed from a drug solution in water. In the case of aplidine, a 40% (v/v) t-butanol/water mixture is preferably used as freeze-drying medium. Although previously described (e.g. rhizoxin), freeze-drying from a 40% t-butanol/water mixture is not common practice.

[0018] In conclusion, the combination of lyophilisation of a drug from a t-butanol/water mixture and the subsequent reconstitution of the lyophilized product with 15/15/70% (v/v/v) Cremophor EL/ethanol/water is unique.

Claims

1. A pharmaceutical composition of a didemnin compound, comprising firstly a lyophilised didemnin preparation including water-soluble material and secondly a reconstitution solution of mixed solvents.

2. A didemnin composition according to claim 1, intended for reconstitution for administration to patients as an antitumor treatment.

3. A didemnin composition according to claim 1 or 2, wherein the didemnin is chosen from didemnins, dehydrodidemnins, nordidemnins, didemnin congeners and didemnin analogs.

4. A didemnin composition according to claim 3, wherein the didemnin compound is aplidine.

5. A didemnin composition according to any preceding claim, wherein the reconstitution solution comprises an alkanol/water mix.

6. A didemnin composition according to claim 5, wherein the reconstitution solution includes a non-ionic surfactant.

7. A didemnin composition according to claim 6, wherein the nonionic surfactant is 10 to 25% v/v of the solution; the alkanol is ethanol and is 10 to 25% v/v of the solution; and the water is 50 to 80% v/v of the solution.

8. A didemnin composition according to any preceding claim, which comprises a vial of lyophilised didemnin preparation including a water-soluble bulking agent, and a separate vial of a premix of non-ionic surfactant/ethanol/water.

9. A method of preparing a pharmaceutical composition of a didemnin compound, which comprises freeze drying a didemnin / water-soluble additive / alkanol / water mix to provide a lyophilised first component, and separately providing an alkanol/water mix as reconstitution solution.

10. A method according to claim 9 wherein the alkanol in the mix is t-butanol.

11. A method according to claim 9 or 10 wherein the amount of alkanol in the alkanol/water mix is 25 to 60% v/v.

Patentansprüche

1. Pharmazeutische Zusammensetzung mit einer Didemninverbindung, umfassend erstens eine lyophilisierte Didemninzubereitung einschließlich wasserlöslichen Materials und zweitens eine Rekonstitutionslösung mit gemischten Lösungsmitteln.

2. Didemninzusammensetzung nach Anspruch 1, vorgesehen zur Rekonstitution für Verabreichung an Patienten als Antitumorbehandlung.

3. Didemninzusammensetzung nach Anspruch 1 oder 2, wobei das Didemnin aus Didemninen, Dehydrodidemninen, Nordidemninen, Didemningattungsverwandten und Didemninanalogen ausgewählt ist.

4. Didemninzusammensetzung nach Anspruch 3, wobei die Didemninverbindung Aplidin ist.

5. Didemninzusammensetzung nach einem der vorhergehenden Ansprüche, wobei die Rekonstitutionslösung eine Mischung Alkanol/Wasser umfaßt.

6. Didemninzusammensetzung nach Anspruch 5, wobei die Rekonstitutionslösung ein nichtionisches grenzflächenaktives Mittel einschließt.

7. Didemninzusammensetzung nach Anspruch 6, wobei das nichtionische grenzflächenaktive Mittel 10 bis 25 Vol.-% der Lösung ausmacht; der Alkanol Ethanol ist und 10 bis 25 Vol.-% der Lösung ausmacht und das Wasser 50 bis 80 Vol.-% der Lösung ausmacht.

8. Didemninzusammensetzung nach einem der vorhergehenden Ansprüche, welche ein Fläschchen mit lyophilisierter Didemninzubereitung einschließlich eines wasserlöslichen Ballastmittels und ein gesondertes Fläschchen mit einer Vormischung mit nichtionischem grenzflächenaktiven Mittel/Ethanol/Wasser umfaßt.

9. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung mit einer Didemninverbindung, welches Gefriertrocknen einer Mischung Didemnin/wasserlöslicher Zusatzstoff/Alkanol/Wasser, um eine lyophilisierte erste Komponente bereitzustellen, und gesondert Bereitstellen einer Mischung Alkanol/Wasser als Rekonstitutionslösung umfaßt.

10. Verfahren nach Anspruch 9, wobei der Alkanol in der Mischung t-Butanol ist.

11. Verfahren nach Anspruch 9 oder 10, wobei der Anteil von Alkanol in der Mischung Alkanol/Wasser 25 bis 60 Vol,-% beträgt.

Revendications

1. Composition pharmaceutique d'un composé de didemnine, comprenant premièrement une préparation d'une didemnine lyophilisée incluant une matière soluble dans l'eau et deuxièmement une solution de reconstitution de solvants mélangés.

2. Composition de didemnine suivant la revendication 1, destinée à une reconstitution pour une administration à des patients en tant que traitement antitumoral.

3. Composition de didemnine suivant la revendication 1 ou 2, dans laquelle la didemnine est choisie parmi des didemnines, des déshydrodidemnines, des nordidemnines, des congénères de didemnine et des analogues de didemnine.

4. Composition de didemnine suivant la revendication 3, dans laquelle le composé de didemnine est de l'aplidine.

5. Composition de didemnine suivant l'une quelconque des revendications précédentes, dans laquelle la solution de reconstitution comprend un mélange d'alcanol/eau.

6. Composition de didemnine suivant la revendication 5, dans laquelle la solution de reconstitution inclut un tensioactif non ionique.

7. Composition de didemnine suivant la revendication 6, dans laquelle le tensioactif non ionique est de 10 à 25% v/v de la solution; l'alcanol est de l'éthanol et il est de 10 à 25% v/v de la solution; et l'eau est de 50 à 80% v/v de la solution.

8. Composition de didemnine suivant l'une quelconque des revendications précédentes, qui comprend un flacon d'une préparation de didemnine lyophilisée incluant un agent gonflant soluble dans l'eau, et un flacon séparé d'un pré-mélange de tensioactif non ionique/éthanol/eau.

9. Procédé pour la préparation d'une composition pharmaceutique d'un composé de didemnine, qui comprend la lyophilisation d'un mélange de didemnine/additif soluble dans l'eau/alcanol/eau pour donner un premier composant lyophilisé et la fourniture séparée d'un mélange d'alcanol/eau en tant que solution de reconstitution.

10. Procédé suivant la revendication 9, dans lequel l'alcanol dans le mélange est du t-butanol.

11. Procédé suivant la revendication 9 ou 10, dans lequel la quantité d'alcanol dans le mélange d'alcanol/eau est de 25 à 60% v/v.